SUMMARY MINUTES

OF THE

CIRCULATORY SYSTEM DEVICES

ADVISORY PANEL MEETING

OPEN SESSION

March 4-5, 2002

Gaithersburg Marriott Washingtonian Center
9751 Washingtonian Boulevard
Gaithersburg, MD

CIRCULATORY SYSTEM DEVICES ADVISORY PANEL MEETING

March 4-5, 2002

Attendees

Acting Chairperson
Warren K. Laskey, M.D.
University of Maryland School of Medicine

Executive Secretary
Lesley Ewing, M.D.
Food and Drug Administration

Voting Members
Salim Aziz, M.D.
University of Colorado

Janet T. Wittes, Ph.D.
Statistics Collaborative, Inc.

Consultants
James A. DeWeese, M.D.*
University of Rochester

Jeffrey Brinker, M.D.+
The Johns Hopkins Hospital

Anthony Comerota, M.D.*
Temple University

Tony W. Simmons, M.D. +
Wake Forest University

Michael J. Domanski, M.D.
National Institutes of Health

Mark Haigney, M.D. +
Uniformed Services University of Health Sciences

Francis Klocke, M.D.*
Northwestern University Medical School

Mitchell Krucoff, M.D. +
Duke University Medical Center

Ileana Pina, M.D.
Case Western Reserve University

Steven Nissen, M.D.
The Cleveland Clinic

Marvin Konstam, M.D.
New England Medical Center

Pilar Ossorio, Ph.D., J.D.
University of Wisconsin

Consumer Representative
Robert Dacey

Patient Representative
Joseph Knapka, Ph.D.

Industry Representative
Michael Morton
Alcon Laboratories

Food and Drug Administration

Bram Zuckerman, M.D.
Michael Berman, Ph.D.
Julie Swain, M.D.
Gerry Gray, Ph.D.
Doris Terry
Helen Barold, M.D.

*attending only March 4
+attending only March 5

OPEN SESSION—March 4, 2002

Call to Order

Acting Chairperson Warren K. Laskey, M.D., called the meeting to order at 10:03 a.m. and read the charge to the panel, which was to consider a supplement to premarket approval application (PMA) P920014/S016 for Thoratec Corporation's HeartMate VE LVAS. **Panel Executive Secretary Lesley Ewing, M.D.,** read the conflict of interest statement, noting that matters concerning Drs. Salim Aziz, Francis Klocke, and Marvin Konstam had been considered but their full participation would be allowed. Drs. James A. DeWeese and Anthony Comerota had declared institutional interests potentially affected by the day's deliberations interest, but their full participation would be allowed. **Dr. Laskey** asked the panel members to introduce themselves and state their areas of expertise**. Dr. Ewing** then read appointments to temporary voting status for Drs. Pilar Ossorio, Michael J. Domanski, James A. DeWeese, Francis Klocke, and Anthony Comerota, and an appointment as acting panel chairperson for Dr. Laskey for the meeting**. Dr. Ewing** noted that Drs. Steven Nissen, Ileana Pina, and Marvin Konstam were voting members or consultants for advisory committees of the Center for Drug Evaluation and Research.

Open Public Hearing

There were no requests to address the panel.

Sponsor Presentation—PMA 910014/S016

Donald A. Middlebrook of Thoratec Corporation thanked the FDA and panel and explained that the PMA supplement sought FDA approval to expand the current indications for use of a left ventricular assist device (LVAD) with patients awaiting cardiac transplantation to include patients with end-stage left ventricular failure who are

ineligible for cardiac transplantation. The PMA contained results from the Randomized Evaluation of Mechanical Assistance in the Treatment of Congestive Heart Failure (REMATCH), which was a landmark randomized controlled trial of the device versus optimal medical management conducted by cooperative agreement between the sponsor, NIH/NHLBI, and Columbia University.

Victor Poirier of Thoratec gave an overview of the device, summarizing changes made to prevent kinking and suture problems. He presented statistics on device reliability based on long-term in vitro testing that showed a 3.1-year estimated mean time to failure and a 76% chance that the device would be free of critical failures at two years. He acknowledged that in vivo results were not as good but suggested that comorbidity and patient management factors were to blame for the less favorable clinical experience.

Eric Rose, M.D., principal investigator for REMATCH, sketched the history and design of the REMATCH trial, a multicenter controlled trial which randomized 129 patients with end-stage heart failure who were ineligible for cardiac transplantation into a device group to receive a left ventricular assist device (LVAD) or optimal medical management (OMM). Patients and physicians were not blinded to treatment assignment. An intent to treat analysis using Kaplan-Meier and Log rank methods was used to assess the key efficacy objective of survival, with safety measured by adverse event and device malfunction rates in the context of a highly ill population. Secondary endpoints included quality of life, functional status, time in/out of hospital, and cardiovascular mortality. Dr. Rose listed techniques used to control bias and stated that key study assumptions were that patients and clinicians would not adopt LVAD unless all-cause mortality over two years was reduced by 1/3 or more and that quality of life with LVAD should equal or

exceed that of the OMM group. The study was powered for survival, and the stopping point was based on number of deaths, not patients enrolled. He emphasized that the trial was not stopped early but stopped when the predetermined number of deaths was reached. Patients were randomized in a one-to-one ratio by study center.

Dr. Lynne Warner Stevenson, a study investigator and chair of the Medical Management Committee, presented information on the REMATCH patient population in the context of the heart failure population. She outlined REMATCH eligibility criteria and explained the reasons why these patients were not transplant candidates, which was predominantly because of age and/or diabetes. After presenting statistics on REMATCH therapies at baseline, ACEI intolerance and renal dysfunction in various trials, REMATCH patient baseline characteristics, other profiles of heart failure in various trials, medical management of the OMM population, and use of IV inotropic agents in the trial, Dr. Stevenson concluded that REMATCH patients define a new profile of severe heart failure. By the time of randomization REMATCH patients had already received "optimal management" and moved beyond medical therapy. She also raised the question of what constitutes a meaningful benefit in end-stage heart disease in terms of percentage of one-year relative benefit or absolute benefit.

Dr. Rose presented clinical results of the REMATCH trial. Baseline characteristics of the two arms showed no real differences. Kaplan-Meier survival analysis illustrating the probability of survival of LVAS versus OMM patients after 92 deaths revealed a 46% reduction in mortality at two years and a 52% reduction at one year. The predominant cause of death for the control group was heart failure for the control group and sepsis or device failure for the LVAS group. One-year survival rates

doubled for the device group, with an absolute reduction of mortality rate of 27% at one year. Two-year survival rates tripled, and median survival time was 408 days for LVAS patients versus 150 days for the control group. Because all-cause mortality was reduced by 46% in LVAS patients, the primary trial objective of a 33% reduction in mortality was exceeded.

Dr. Rose reported that serious adverse events were more common in the device group, although the rate decreased over time, with the majority being neurologic or bleeding/sepsis events. Neurologic events were more likely to be transient and to occur within 30 days. Experience with bleeding was largely associated with device implant or reimplant and infection was a specific complication of VAD use, with an initially unappreciated association with malnutrition. Of the 156 device malfunctions reported, most dealt with broken lead wires, incompetence of the inflow valve, or a broken Y-connector. Dr. Rose stated that the incidence of overall adverse events was acceptable compared to the natural history of terminal illness, and that sponsors had identified various opportunities for improvement.

The SF-36 Heart Survey, the Minnesota Living with Heart Failure Test, the NYHA functional assessment, the Beck Depression Inventory, and the EuroQOL were used to assess quality of life. Dr. Rose observed that LVAD scores were never worse than the control group except for short-term postoperative pain. LVAD generic quality of life scores were better than control at 12 months in key prespecified SF-36 domains. LVAD disease-specific quality of life scores on the Minnesota Living with Heart Failure Test improved over control at 12 months but were not statistically significant. NYHA functional class improved significantly with device use over control and reduced

depressive symptoms to the normal range, unlike the control group. In context, the LVAD physical function scores were not normal, but were analogous to patients receiving long-term hemodialysis and ambulatory heart failure patients. LVAD emotional–role scores were better than those reported for clinical depression and similar to those for ambulatory heart failure patients.

Dr. Rose also answered questions previously raised by the FDA on device reliability, suggesting modifications to the device for end of pump life indicators. He thought the observed failure rates define what is acceptable now in the context of the available alternative therapies and terminal illness and that the reliability is sufficient to produce survival benefit. Dr. Rose noted that a clinically meaningful benefit in survival had been defined in a prestudy agreement, and that the study results surpassed this figure. He stated that the trends in the quality of life data are consistently favorable, although no benchmarks are available, and that the NYHA class and prespecified physical function domains are significant at 12 months. Dr. Rose also listed proposed post-market surveillance activities.

Dr. Donald A. Middlebrook emphasized that the study presented strong evidence of a clinically meaningful survival benefit, with the VE LVAS providing reasonable evidence for safety in the context of terminal illness. All quality of life instruments showed sustained improvement trends over control and an unprecedented reduction in mortality in end-stage heart failure patients when compared to landmark drug studies, making it the only proven alternative therapy for nontransplantable end-stage heart failure patients.

FDA Presentation

Michael Berman, Ph.D., lead reviewer, introduced the review team and read the proposed expanded indication for use. He described the device components and listed satisfactory elements of the preclinical evaluation. Remaining FDA concerns include the reliability of the internal components and a device end-of-life indicator. Dr. Berman explained the reliability protocol used and results obtained in bench testing, noting a problem still to be corrected in main bearing failures observed at three and a half years. Clinical trial observations also revealed an elevated pump chamber pressure and high beat rate (inflow valve incompetence), and observed pump end of life events were at the low end of reliability predictions made in bench testing. These issues, along with the lack of a device end-of-life indicator, raised concerns because device replacement requires major surgery.

Julie Swain, M.D., presented the clinical review. The study design assumptions were based on mortality at two years as presented in clinical literature, with the power calculated for 92 study deaths and 128 patients enrolled. She described inclusion and exclusion criteria and study design. Dr. Swain presented survival statistics showing that at 27 months, four out of seven device patients died and three out of three control patients died. Serious adverse event data, however, showed 64 out of 68 device patients experienced a serious event, compared to 38 out of 61 control patients. Comparing destination and bridge therapy adverse events was not helpful because of differences in patient populations, definitions, and patient care teams. Dr. Swain presented bar graphs on these adverse events by neurological dysfunction, local infections, sepsis, and

bleeding. Analysis of device malfunctions showed high rates of mortality. Rates of withdrawal from treatment were roughly similar for the two groups.

For secondary endpoints, Dr. Swain presented NYHA class results showing that LVAS patients significantly improved at 6 and 12 months. However, she questioned the effect on physicians and patients of not being selected for the study and noted that the placebo effect of device use in the unblinded study might be important. She thought there should be consistency between NYHA, quality of life, six-minute hall walk, and peak VO2 results. Peak VO2 results and length of hospitalization, however, did not show significant improvement for the LVAS patients over control. She concluded that LVAS use did produce a survival benefit in a very advanced heart failure population, but the mortality and morbidity associated with its use were considerable. Interpretation of the functional testing data is limited by the small amount of data available.

Gerry Gray, Ph.D., statistical reviewer, synopsized the study, noting that the trial was designed to stop at 92 deaths and that there was complete follow-up for survival analysis. He showed graphs indicating a significant difference in mortality for the device arm at the one-year point, a significant increase in median survival time for the device group of 405 days as opposed to 150 for control, and a significant difference between Kaplan-Meier survival curves favoring the device. However, the serious adverse event rates were much higher in the device arm; he noted that device treatment resulted in decreased cardiac mortality rates and increased non-cardiac mortality rates. Survival past two years was poor in both groups, with some indication of a relative drop-off in LVAS survival at 22 months, although there were few patients. The numbers of adverse and serious adverse events per person and per 100 patient days were significantly greater for

the device arm than for control arm, however, and he asked the panel to weigh the survival benefit versus the adverse event rate. The difference between control and device groups was almost entirely in the time to first event, not time between subsequent events, and the odds of death versus serious adverse event were always higher for the control group. Analysis of functional status favored the device group, but not consistently.

Michael Berman read the FDA questions for panel review.

Open Committee Discussion

Lead panel reviewer Marvin Konstam, M.D., congratulated the sponsors and FDA review team on a landmark study but had several areas of concern. The first involved whether the primary endpoint had been met, given that there was not significant improvement in mortality at two years. Sponsors replied that the study was designed, per agreement with the FDA, to provide observation over a two-year period rather than a single, discrete endpoint at two years. His second concern involved the clinical relevance of the device if most patients are dead at two years and whether unreliability of the device contributed to this mortality. The third area of concern involved the quality of life assessment, which he found partially reassuring and partially confusing because of the high dropout rate and the criteria selected. Fourth, he expressed concern about the high number of neurological events and bleeding problems, suggesting that anticoagulation therapies needed further attention. Finally, he asked for a clearer indication of the intended population of use, given the limited number of those alive at two years and the large number of adverse events.

Lead panel reviewer Salim Aziz, M.D., praised the company for involving academia as well as industry and NIH in the study. He asked for further information on

the etiology of the grand mal seizures, expressing concern about the need for metabolic control of surgical patients. The problem of sepsis was multi-factorial, but he suggested attention to albumin levels and preoperative nutrition. Dr. Aziz stated that he was not convinced that the device could be used as a destination therapy, despite its success as a bridge therapy, and questioned its duration to four years.

Other members of the panel raised questions involving plans for follow-up to provide more data on device failure and ways to prevent device-related sepsis. Several panel members panel wanted more in vivo and in vitro data on the mean time to device failure. Concerns were expressed about the quality of life data, including investigator bias, the small numbers used, and the unblinded nature of the trial. It was suggested that sponsors present data for both control and device on rates of death and cerebrovascular accidents at one year rather than simply mortality. Several members stated that an independent outsider not involved in the study should have made the assessment of NYHA classification. The high rate of infection for the device group prompted considerable panel discussion; it was suggested that sponsors look more closely at malnutrition and also at female versus male immune responses or differences in racial or ethnic response to treatment. Others asked about correlation of outcome to age and if a risk profile for sepsis or CVA could be developed. Issues of informed consent and non-resuscitation orders also needed attention. A training program for physicians and for patients was recommended.

Consumer Representative Mr. Dacey suggested simplification of the language used in the patient information. **Industry Representative Mr. Morton** observed that

many other heart prostheses do not have an end-of-device-life indicator, and that this device should not be held to an unfair standard.

FDA Questions to the Panel

Device Reliability

1. *The bench testing performed to assess device reliability did not account for all observed clinical conditions. Accordingly, the observed times to device failure and device malfunction seen in the clinical study are less than those predicted by the reliability model. As well, there is no reliable end-of-pump-life indicator. Please discuss the clinical implications of the observed device reliability.*

The panel asked for more data on device reliability, in particular distribution of time to failure (all data points), given that the clinical reliability to date fell short of that seen in the in vitro testing.

2. *Are the device failure and malfunction rates and their time to occurrence appropriate for a device intended for use for destination therapy?*

There was no panel consensus on this issue. Some panel members said the device was not appropriate as destination therapy, given the failure rates. Some asked for clarification on destination therapy. Others said there was insufficient data to decide, particularly asking for mean and median time to failure and actual distribution of those data points.

Data Analysis

3. *Given the Kaplan-Meier survival curves and the fact that seven device patients and three control patients as of 2/02 had survived to 24 months, have enough patient data been reported to demonstrate a clinically meaningful survival benefit?*

The panel had a range of answers. Some stated there were unknown data in the pipeline and insufficient data reported to answer. Another viewpoint was that the device could be approved as safe and efficacious to extend life by one year. Other members disagreed, saying that the device might extend life by one year but with inconsistent results for quality of life, high rates of hospitalization, and high failure rates. There was considerable philosophical discussion between those reluctant to deny the possibility of increased survival to patients who were made aware of the potential risks of adverse events and those who found the quality of life benefits debatable and the risk of adverse events too high for a one-year improvement in survivability. After FDA clarification of what the agency meant by some idea of a clinically meaningful survival benefit, Dr. Laskey pointed out that an index of survival benefit showing how many days or months a patient can expect is possible but said it was difficult to divorce survival from quality of life and adverse events.

Effectiveness of the System on Functional Status

4. *The NYHA, QOL, and functional testing results are not consistent. From these data, can we determine that there is a clinically meaningful improvement in functional status?*

The panel consensus was that while they would like to read into these results an improvement in functional status, it was difficult to conclude definitively that there had been such an improvement, given problems with lack of blinding, investigator bias, and possible placebo effect. The panel recommended that NYHA classification assessment always be done by a third party not involved with the study.

Risk-Benefit of the System used for Destination Therapy

5. *This device demonstrated an increase in medial survival time and showed an overall difference in survival. However, this benefit diminished at two years and was associated with serious adverse events and hospitalizations throughout the course of the study. Do the benefits of this device outweigh its risks?*

There was no panel consensus on this issue. All agreed that the risks are real and evident, but the ratio of risk to benefit is unclear, given that there are concerns about both numerator and denominator.

Labeling

6. *Please discuss the appropriateness of the proposed indications for use for this device.*

   The panel recommended that there should be more detailed information in the indications: all complications should be enumerated and all risks discussed as well as careful delineation of those for whom the device is and is not indicated. It should be stressed that the device is only indicated for the severely ill with a limited life expectancy

   b. Does the labeling accurately inform patients of the risks of the device?

   The panel recommended conspicuous warnings on the risks of mechanical failure as well as infection and ways to minimize or manage risk of infection. Members urged the FDA and sponsors to work together both on wording and on patient training.

   c. Does the labeling adequately inform patients of the expected duration of use for this device?

   The panel recommended more patient information on the uncertainty about device reliability and duration. Labeling should state that there is no indication of end of device life and that reimplantation is risky and limited.

d. Are there any other issues of safety or effectiveness not adequately covered in the labeling?

The panel urged that the labeling be blunt in stating that life expectancy is not known.

Post-Market Evaluation

7. *Do you believe that additional clinical follow-up or post-market studies are necessary to evaluate the long-term effects of this device?*

The panel recommended additional post-market studies on which patients will benefit and which will not, on internal device malfunction, on lack of predictability, on the time course of different types of complications, on anticoagulation regimens, and on additional ascertainments of endpoints.

Open Public Hearing

There were no requests to speak.

Closing Sponsor Comments

The sponsors thanked the panel, FDA, and presenters for their remarks.

Recommendations and Vote

Dr. Ewing read the panel the regulatory definitions and voting instructions. A motion was made by Dr. Konstam and seconded by Dr. Comerota to recommend the PMA as approvable with the following conditions:

1a) Additional analysis of existing data from the current data set should be performed pertaining to device reliability at two years. This condition passed.

1b) Analysis of time to death or stroke should be made performed on the existing data set to see if it is consistent with the current survival analysis. This condition passed.

2) The patient population indicated for the device should be more clearly delineated. This condition passed.

3) Rigorous criteria for implantation for both surgeon and facility regarding patient selection, surgeon expertise, and follow-up should be established. The FDA should ensure that the training is rigorous and that procedures are performed in centers and by individuals highly trained with patients in end-stage heart failure. This condition passed.

4) A registry should be established for postmarket surveillance, with an independent evaluator to assess rates of survival; life expectancy; post-implantation reliability including device failure, durability and longevity; and adverse events, including thrombo-embolytic events. This condition passed.

5) There should be a detailed set of patient information delineating the trade-off between survivability and adverse events and major complications, with an indication of patient functioning. The patient information package should clarify risks and outcomes and rates of adverse events and explantation. This condition passed.

The motion to recommend the PMA as approvable subject to the above conditions carried by a vote of eight to two. Those who opposed the motion stated that they did so because they thought the device promising but not yet ready for approval given its internal failure rate.

Open Public Hearing

There were no requests to speak.

Adjournment

After thanking the presenters and FDA review team, **Dr. Laskey** adjourned the Open Session for the day at 5:50 p.m.

OPEN SESSION—MARCH 5, 2002

Call to Order

Acting Chairperson Warren K. Laskey, M.D., called the meeting to order at 8:05 a.m. and read the charge to the panel, which was to consider a premarket approval application (PMA) P010031 for the Medtronic InSync Implantable Cardioverter Defibrillator Model 7272 System. **Panel Executive Secretary Lesley Ewing, M.D.,** read the conflict of interest statement, noting that a limited waiver had been granted for Dr. Tony Simmons for his interest in firms that could potentially be affected by the panel's recommendations. The waiver allowed Dr. Simmons to participate only in the panel discussion. Other matters regarding Drs. Simmons, Salim Aziz, Mitchell Krucoff, Jeffrey Brinker, Mark Haigney, and Marvin Konstam were considered but deemed unrelated and their full participation was allowed. **Dr. Laskey** asked the rest of the panel to introduce themselves and state their areas of expertise. **Dr. Ewing** then read appointments to temporary voting status for Drs. Pilar Ossorio, Michael J. Domanski, Steven Nissen, Ileana Pina, Marvin Konstam, Mitchell Krucoff, Mark Haigney, and Jeffrey Brinker and an appointment as acting panel chairperson for Warren K. Laskey, M.D., for the duration of the meeting. **Dr. Ewing** noted that Drs. Steven Nissen, Ileana Pina, and Marvin Konstam were voting members or consultants for advisory committees of the Center for Drug Evaluation and Research.

Open Public Hearing

There were no requests to address the panel.

Sponsor Presentation

Dr. William T. Abraham, study investigator, provided background on ventricular dysynchrony and cardiac resynchronization (CRT) and explained the design of the original InSync trial, which was a prospective, randomized, double-blind trial comparing candidates for cardiac resynchronization with no indication for an ICD in a device group with activated CRT to an implanted group without activated CRT at the one, three, and six month follow-up points, with later crossover to CRT for the control. Primary endpoints, which included improvement in quality of life, NYHA class, and six-minute walk, were all met. Secondary endpoints, which were peak VO2, exercise time, and composite response, also markedly improved. Primary safety results, which included implant success; low complication rates for device, leads, and pacing system; and attainment of prespecified pacing thresholds, were all met. Dr. Abraham then explained the background of the InSync ICD device trial, which sought to ensure that patients with an ICD indication responded favorably to resynchronization and that the coexistence of resynchronization did not adversely affect ICD function. Patients were randomized into a control group with the pacing mode off or a device group with the pacing mode on.

Dr. James Young, study investigator, explained the study design, methodology, and patient population of the InSync ICD trial, comparing entry criteria, study design, and timing of baseline tests to the original InSync trial and explaining the blinding procedures. The three primary effectiveness endpoints were the change from baseline to six months in quality of life score (Minnesota questionnaire), NYHA classification, and six-minute hall walk distance for device as compared to control group (implanted with device with CRT off and ICD active), using the Hochberg adjustment for multiplicity.

Secondary effectiveness endpoints included exercise performance, clinical composite response, health care utilization, echocardiographic variables, QRS duration, and neurohormonal variables. The primary study cohort consisted of 421 NYHA Class III and IV patients (176 control and 186 device), although class II patients were also admitted and studied separately. Results were presented based on an intention to treat analysis for patients with paired data at baseline and six months, including crossovers, with a last observation carried forward analysis. Patient baseline demographics for control and device groups were roughly similar.

Dr. Angel Leon, study investigator, presented the safety results. Primary objectives were survival with freedom from device-, lead-, and system-complications. Secondary safety objectives were characterization of patient survival, complications, and observations. Lead effectiveness objectives were implant success, evaluation of the electrical performance of the leads, spontaneous VT/VF therapy effectiveness, comparison of VT/VF event rates in the two arms, and biventricular ATP therapy effectiveness. All primary safety objectives were satisfied, and secondary safety objectives were within prescribed bounds. Lead effectiveness results were within the statistically defined parameters.

Dr. Young presented effectiveness results. The change in quality of life score showed a highly significant improvement from baseline to six months for the device group as compared to control. Change in NYHA functional class also favored the device group, although not at as high a level of statistical significance. Differences in six-minute hall walk distance did not achieve statistical significance. Clinical endpoints such as

exercise performance, clinical composite response, and healthcare utilization showed favorable trends but did not achieve statistical significance.

Dr. Abraham compared the InSync and InSync ICD trials, which were designed to be nearly identical, with the exception of performing the cardiopulmonary exercise tests post-implant in the InSync ICD trial. The populations of the two trials were very similar with the exception of a higher percentage of those with heart failure of ischemic origin in the ICD study. Changes in quality of life score for the two trials showed a similar pattern of improvement for the device group and a similar magnitude of change, as did the change in NYHA class. The change in six-minute hall walk, which showed a highly significant improvement in the InSync trial for device over control, showed far less improvement for the InSync ICD trial results. A comparison of the primary endpoints and secondary clinical endpoints for the InSync and InSync ICD studies showed strikingly similar results between the two studies, with similar improvement. Comparison of the risk of death or worsening heart failure favored device over control for the InSync ICD, with a favorable but less significant results for the InSync trial in a posthoc analysis. Dr. Abraham concluded that the benefits of resynchronization in patients with an ICD indication are similar in both direction and magnitude to the effects seen in patients without an ICD indication.

FDA Presentation

Doris Terry acknowledged the FDA review team and outlined the regulatory history of the modular PMA. She described the InSync ICD model 7272 system components, the preclinical testing performed on the model, software validation, and preclinical testing on the leads. All these results met the acceptance criteria.

Dr. Helen Barold presented the FDA clinical summary. She read the proposed indication for use and explained randomization and timing of testing. Patients and CHF physicians or staff were blinded; EP physicians were unblinded. Dr. Barold listed the three co-primary effectiveness endpoints and the three primary safety objectives, as well as all secondary objectives. She read the inclusion and exclusion criteria and delineated the patient accountability for the 362 NYHA III/IV patients randomized, noting that 71 (20%) were "administratively censored." There were a number of protocol deviations from blinding and 25 patients who crossed over from CR off to on. Baseline characteristics of the control and device group were roughly similar, with the majority being NYHA Class III older male patients.

Dr. Barold presented the safety results on an intent to treat basis, noting that the quality of life results showed a large improvement in both device and control group but with a larger improvement in the device group. Change in NYHA classification also was more prevalent in the device group, although not at the same level of statistical significance. Six-minute hall walk results, however, showed little difference. Thus, the device met the third criterion of the Hochberg adjustment for multiplicity. On the primary endpoint of LV lead effectiveness, Dr. Barold noted a 10% implant failure rate and noted that FDA has not yet reviewed materials requested on a breakdown of Class II and IV patients.

Secondary objectives such as CHF composite showed an improvement of treatment group over control group, but no difference in patient global assessment score. There were no differences in hospitalization. Echocardiographic results and neurohormones showed no difference between the groups, although the neuroepinephrine

level showed an unfavorable trend in the device group. Mortality rates for the two groups were very similar. Observed adverse event rates for both groups produced unremarkable results, although there was a higher rate for the unexplained "other" grouping for device.

Dr. Barold noted that FDA has requested information on VF detection time to ensure that the addition of biventricular pacing does not interfere with the ability to sense VF and to ensure that the left ventricular lead and/or biventricular pacing is not responsible for inappropriate shocks. FDA has also requested information to see if ICD programming interferes with continuous biventricular capture. She listed a number of programming issues involving device-device interaction and limitations for consideration.

Doris Terry read the FDA questions for panel review.

Open Committee Discussion

Lead panel reviewer Dr. Ileana Pina had several questions for the sponsors, including the incidence of sudden death and whether these deaths were linked to ineffective shocks. She also asked about the quality of life information and the relationship to rate of hospitalization. Dr. Pina asked whether it was possible to predict lead dislodgment or lead implant failure by correlation with lead diameter or NYHA class function and if subgroup analysis would be useful. Dr. Pina also asked for clarification about blinding procedures during the cardiopulmonary tests and about medication therapy involving initiation of beta blocker use during the trial.

Lead panel reviewer Dr. Mark Haigney congratulated the sponsors on their study but raised concerns about the small magnitude of effects seen and raised issues about blinding procedures and possible placebo effects on the quality of life data. He

asked whether subgroup analysis had identified which patients benefited the most and if they could now be identified in advance before therapy. Dr. Haigney urged in particular that subgroup analysis be done on correlation of QRS with magnitude of effect on quality of life. He asked about placing of the lead in the lateral wall position and correlation of lead position with outcome or treatment effect. He also favored a postmarketing study on how long the lead could function. Dr. Haigney concluded that the device appeared to be effective at converting VT and VF but could lead to inappropriate shocks and was less effective in cardioversion of fast VT from the coronary sinus and right ventricle.

Statistical concerns raised by the panel involved how to deal with the co-endpoints and the administrative censoring, as well as whether the protocol of stopping at 224 patients was prespecified with the FDA. Members of the panel differed in the level of their concerns about blinding procedures in the trial. Several asked for greater subgroup analysis. Inappropriate shocking was a concern as a part of the risk/benefit ratio. It was suggested that the trial population should have included more women and people of color. One panel member asked for more information on the electrical safety of the device and on how the device was programmed. Issues of investigator bias because of the high number of crossovers from control to device group were a concern, as were training issues and the learning curve involved with device implantation.

FDA Questions to the Panel

Study Design and Analysis Method

1) Please address the following issues:

a. *Are there any concerns related to the "administrative censoring" of 20 % of the enrolled patients who had not passed the six-month point at the time of the submission?*

The panel expressed repeated concerns about the missing data on the 20% of the enrolled patients. The panel agreed that the decision to stop the study at the predetermined point was a major concern for them.

b. *Please discuss the benefits and limitations associated with the six-month follow-up duration for the primary endpoints.*

The duration of the follow-up was not an issue for the panel so much as the robustness of the data collected, about which there was divided sentiment.

c. *Please discuss any concerns about the propensity for crossovers and any additional issues that may be related to blinding.*

The panel expressed uneasiness with the propensity for crossovers and for what lay behind that propensity, whether it was investigator bias or lack of blinding.

d. *The intent-to-treat analysis on NYHA class, quality of life, and 6-minute hall walk produced nominal p-values of .027, .009, and .407, respectively. Thus, the study results meet the prespecified Hochberg criteria for statistical significance in that one of the endpoints (quality of life) produced a p-value less than .0167. In light of this, please comment on the possible interpretation of the results for each of the co-primary endpoints individually.*

There was a long discussion about the individual p-values and the Hochberg criteria, with the panel aware of the strengths and benefits of a combined endpoint analysis, but the

panel sought to move beyond that issue to discuss what the data signified statistically and how to correlate that significance to clinically meaningful results.

In answer to a follow-on question from the FDA about upcoming new trials, the panel emphasized that they prefer complete data sets but can cope with incomplete data sets if they are given better endpoints and tools for analysis as they grapple with devices in new areas.

Effectiveness of the System in Treating CHF

2. *The primary endpoints of the study were improvement in NYHA class, quality of life, and six-minute hall walk. Please discuss the clinical relevance of these endpoints for evaluating a therapy for congestive heart failure (CHF).*

The panel thought there was a discordance within the scientific community over the three measures, but that they would have to live with that unhappiness until there are more precise tools. It was noted that the tremendous scatter of results and noise would diminish as a study gets larger.

3. *Please discuss the clinical relevance of the sponsor's choice of secondary endpoints for evaluating a therapy for CHF. Are there specific secondary endpoints, such as peak VO2, that should be more heavily weighted in the assessment of the device?*

The panel did not find any of these endpoints conclusive and noted that many others were discussed in the last panel meeting on the InSync device, such as echocardiographic assessment or change in mitrocardial regurgitation. Some panel members emphasized that the dialogue over endpoints and denominators should occur early, in the pre-IDE stage, because a prospective clinical trial has to be evaluated by its design. In answer to an FDA request for clarification, the panel added that there is no non-mortality endpoint

that is consistently compelling across trials and that multivariate endpoints are acceptable.

4. *Please comment on whether the results of the clinical study support the effectiveness of the device for the treatment of patients with medically stable Class III/IV CHF.*

Concerns remained that the data set was incomplete and failed to answer all issues, but a slim majority thought the results within the constraints of the prespecified and multiple endpoints supported efficacy of the device.

Safety of the System in Treating CHF

5. *When evaluating the safety of the device, one concern is whether the treatment contributes to the worsening of CHF. Please comment on whether the results support the safety of the system for treating CHF in the population studied.*

The consensus of the panel was that there was no evidence that the treatment worsens CHF within the six-month timeframe. Beyond six months, there were no data.

Effectiveness of the System as an ICD

6. *Please comment on whether the sponsor has provided adequate information to assure that there is no interference of proper ICD functionality with the addition of biventricular pacing, and that both biventricular pacing and ICD therapy can be delivered simultaneously.*

The panel stated that they had insufficient data in this area to answer the question, including rates of inappropriate shocking.

7. *Please discuss whether you have any comments or recommendations regarding programming considerations for the device.*

Various ideas were suggested such as a relative contraindication for device use with very slow ventricular tachycardia, but ultimately the panel agreed that they had insufficient data to answer this question and recommended more data collection.

Safety of the System

8. *Please comment on whether the results provide a reasonable assurance of the safety of the Model 7272 ICD pulse generator.*

The panel had no concerns about the safety of the pulse generator.

9. *Please comment on whether the results provide a reasonable assurance of the safety of the Model 4189 lead.*

The panel recommended that more information be gathered on lead-related complications.

Safety of the System

10. *The sponsor has provided analyses of the system-related complications at six months and the adverse events (complications and observations) reported in the clinical study. Please comment on whether the results provide a reasonable assurance of the safety of the InSync ICD System.*

The panel recommended a plainer explanation of the data and said that they were unsure what the risk of reoperation was and what patient expectations should be with the average practitioner. The data should be structured with recognition that the indicated population warrants ICD placement and with attention to what else is needed to structure biventricular pacing.

Risk-Benefit of the System for Treatment of CHF

11. *Please discuss the overall risk-benefit of the system.*

The panel remained concerned with the numerator, saying that its magnitude was still unclear.

Labeling

12. If you recommend approval of the device, please address the following questions,

a. Do the Indications for Use adequately define the patient population studied?

In addition to the proposed indications, the panel recommended two additional bullets stating that

- ?? This device is intended for people requiring an ICD
- ?? This device in the setting of heart failure improves quality of life and may improve NYHA classification.

b. Based on the clinical experience, should there be additional contraindications, warnings and precautions for the use of the InSync Model 7272 ICD System?

The panel recommended that the warnings should include the additional risk compared to an ICD in terms of the lead. It should also be stated that the benefits of this device are known to extend to six months.

c. Please comment on the operator instructions as to whether they adequately describe how the device should be used to maximize the benefits and minimize adverse events.

The panel recommended operator training similar to that required for the InSync device, to include a didactic program, use with animal models, and a center for training.

Labeling

d. Please provide any other recommendations or comments regarding the labeling.

The panel had no additional remarks.

Post-Market Study

13. With approval of the Medtronic In Sync biventricular pacing system FDA and the sponsor agreed on the following post-approval conditions: a) obtaining 12-month mortality data on the IDE cohort, and b) performing a three-year evaluation of mortality and chronic lead performance, including electrical performance and adverse events, on 1,000 patients. If you recommend approval, please comment on whether additional clinical follow-up or post-market studies are necessary for this device.

This question was deferred until the vote.

Closing Sponsor Remarks

Sponsor representatives thanked the panel and added that further documentation requested would be provided on the interaction between biventricular pacing and the ICD. They added that there is a meaningful clinical effect with device use, not just a statistically significant effect, for these two overlapping populations.

Closing Comments from the Consumer and Industry Representatives

Consumer Representative Robert Dacey noted that more work is being done to define quality of life, which is a core issue for this population. He urged the sponsors to simplify the patient manual.

Open Public Hearing

There were no requests to speak.

Panel Recommendations and Vote

Dr. Ewing read the panel the regulatory definitions and voting instructions. A motion was made by **Dr. Pina** and seconded by **Dr. Konstam** to recommend the PMA as

not approvable because the data set did not provide a concordance of data showing benefits for patients who need an ICD. She also stated concerns over the amount of patients who had crossover and that fact that the improvement in quality of life may reflect a small number of patients who received real benefit from the therapy. This motion initially resulted in a tie, which **Acting Panel Chairperson Dr. Laskey** resolved by voting against the motion, which then failed.

A motion was then made by **Dr. Nissen** and seconded by **Dr. Domanski** to recommend the PMA as approvable subject to the following conditions:

1) A postmarketing study as defined in FDA question 13 with 12-month mortality data would be performed. This condition carried unanimously.
2) A data set on the interaction of the ICD function and the synchronization pacing function would be completed and brought to the FDA for review. This condition carried unanimously.
3) The complete data set regarding the safety of the lead and a clearly aggregated combined risk of lead placement failure and in toto device risk should be reported to the FDA. This condition carried unanimously.
4) The sponsor should provide to the FDA in writing documentation of the agreement on the stopping point of the study. This condition carried unanimously.

The motion to recommend the PMA as approvable subject to the four conditions above resulted in a tie vote, which **Acting Panel Chairperson Dr. Laskey** resolved in favor of the motion. The motion thus passed by a vote of six to five.

Dr. Laskey thanked those present and adjourned the Open Session at 3:30 p.m.

I certify that I attended the Open Session of the Circulatory Systems Devices Panel Meeting on March 4-5, 2002, and that this summary accurately reflects what transpired.

_____

Lesley Ewing, M.D.
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

_____

Warren K. Laskey, M.D.
Acting Panel Chairperson

Aileen M. Moodie
9821 Hollow Glen Pl.
Silver Spring, MD 20910
301-587-9722